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SEER Update of Incidence and Trends in Pediatric Malignancies: Acute Lymphoblastic Leukemia

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Background. Acute lymphoblastic leukemia (ALL) represents the most common malignancy of childhood. Its incidence peaks in children just before school entry age; i.e., in 2–3 year olds. It is known to be more common in white children in the USA; the incidence is also higher in boys than girls. ***Procedure.*** We reviewed the 5,379 cases of ALL among persons under 20 years of age in the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database. ***Results.*** The overall incidence of ALL was $26/10^6$ person-years between 1973 and 1998, but increased from $19/10^6$ person-years in 1973–77 to $28/10^6$ person-years in 1993–98 ($P < 0.0001$). Rates were 44% higher among Whites compared to Blacks ($27/10^6$ person-years vs. $15/10^6$ person-years, $P < 0.0001$). In 1992–1998, the incidence rate for Hispanics was $43/10^6$ person-years, significantly higher than non-Hispanics ($28/10^6$, $P < 0.0001$). White children with ALL had better 5-year survival rates than Black children with ALL (71% vs. 58%, $P < 0.0001$), and 5-year survival was poorest among black males. ***Conclusions.*** ALL incidence has increased over the examined 25-year period. The rate in US whites is higher than that of US Blacks, and the rates in the Hispanic subgroup are the highest of all. While the median survival period is now more than 10 years overall, the 5-year survival rate remains poor for Black males under 4 years of age. Socioeconomic factors do not account for this difference, which may relate to ALL subtype distribution. Med Pediatr Oncol 2002;39:554–557. © 2002 Wiley-Liss, Inc.

Key words: acute lymphoblastic leukemia (ALL); epidemiology; SEER

INTRODUCTION

In the United States, acute lymphoblastic leukemia (ALL) is the most common cancer of childhood, yet the published epidemiologic description of ALL is surprisingly sparse [1,2]. Incidence peaks just before school entry, it is more common in White than Black children and incidence is higher in boys than girls [1–3]. These facts derive from overview publications on all pediatric malignancies, the most recent of which was published in 1999 as *The SEER Pediatric Cancer Monograph* [4].

By nature of its summary approach, the *Pediatric Monograph* was constrained from detailed analysis of lingering questions. The treatment of childhood leukemia is one of the greatest success stories of modern pediatric oncology practice, yet the public health impact of survival trends has not been documented. Benefits from treatment advances have not been equally realized by all; the *Pediatric Monograph* documents wide racial differences in summary survival and these differences bear further investigation. The ensuing accrual of many hundreds of cases by the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) program over three additional years provides further scientific motivation to revisit population-based data on ALL.

MATERIALS AND METHODS

The NCI SEER program collects tumor site, histology, and demographics data from all residents who are diagnosed with cancer in collaborating states or localities. Reporting to cancer registries is legally mandated [5]. For most analyses, we used data on patients diagnosed in 1973–98 in the following nine original registries: Connecticut, Hawaii, Iowa, New Mexico, Utah, Atlanta, Detroit, Seattle/Puget Sound, and San Francisco/Oakland. For analyses particular to Hispanic children, we included cases diagnosed in 1992–98 in both the aforementioned original registries, and cases from the Los Angeles and San Jose registries. Reporting has been estimated to be 98% complete or better in each of these eleven registries [6]. Regular follow-up of children with ALL is done both locally and with the National Death Index [7] to ascertain survival status. SEER data for Hispanics with ALL has been collected from 1992–1998, n = 760. The registry in Los Angeles currently contri-

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butes two-thirds of the included cases (n = 503, 66%) and the vast majority of Hispanics are classified as White race (n = 749, 99%). We restricted the analysis to Whites, Blacks, and Hispanics because we did not have sufficient numbers among Asians to make valid statistical conclusions.

We restricted the analyses to persons diagnosed from 1973 to 1998 who were reported to have ALL (M-9821) as coded by the International Classification of Diseases for Oncology, version 2 [8]. Excluded from analysis were persons over 20 years of age at diagnosis, patients with multiple primaries, those cases diagnosed at autopsy or documented by death certificate only and patients without at least 1 month of follow-up. Over the time period, 1973–1998, characterization of leukemic blasts has been aided by our increased knowledge regarding immunophenotyping and karyotyping. This enhanced ability to categorize has helped direct therapeutic interventions. Detailed information regarding sub-classifications was not recorded by SEER during the period under study.

Incidence rates were calculated using SEER*Stat software [9] and expressed as cases per million person-years among the population under 20 years old. Incidence rates were compared under the assumption that the number of incidents follows a Poisson distribution. Observed survivals (from all causes) were calculated using life-table methods (in yearly intervals). Patients were censored at the time of loss to follow-up or December 31, 1998, whichever occurred first. Log-rank type tests were employed to compare survival curves [10]. SAS software package was used for all comparisons [11]. All *P*-values reflect two-sided tests.

RESULTS

There were 4,619 children who had the diagnosis of ALL during the period 1973–1998 in the nine original registries (Table I). The overall incidence of ALL was 26/10^6 person-years between 1973 and 1998, but it increased from 19/10^6 person-years in 1973–77 to 28/10^6 person-years in 1993–98 ($P < 0.0001$). The large increase in ALL incidence rate between 1973 and 1987 was balanced by a decrease in the incidence rate of acute leukemia, not otherwise specified. For the entire 1973–98 period, the ALL incidence rate for persons aged 0–4 years was 52/10^6 person-years, for persons 5–9 years was 26/10^6 person-years, for persons 10–14 years was 15/10^6 person years, and for persons 15–19 was 11/10^6 person-years.

All ethnic groups showed an early peak incidence of ALL with most cases occurring between 2 and 4 years old (Table I). The ratio of affected male/female was 1.3:1. The rates were slightly higher in males (29/10^6) than females (23/10^6, $P < 0.0001$). The majority of patients were white (83%, Table I). Rates were 44% higher among Whites compared to Blacks (27/10^6 person-years vs. 15/10^6 person-years, $P < 0.0001$). Racial differences contrasted sharply when comparing sex-specific incidence: white males had significantly higher ALL incidence than Black males (31/10^6 vs. 16/10^6, $P < 0.0001$), a similar difference was found for White and Black females (24/10^6 vs. 14/10^6, $P < 0.0001$).

Median survival has improved from 3 to 4 years of survival in 1973–79 to greater than 10 years in 1980–1989. The age-specific median survival (in 5-year age groups) for all time periods combined exceeded 10 years with the exception of those patients diagnosed at ages 15–19 years (Table II). White children with ALL had better 5-year survival than Black children (71% vs. 58%, $P < 0.0001$). Among children less than 5 years old, infants had the shortest median survival and progressively longer survivals were seen among children aged 1, 2, 3, and 4 years of age (1.8, > 10, > 10, > 10, and > 10 years, respectively). Black male children aged 3–4 years had a particularly poor 5-year survival compared to other same-aged children (50% vs. 82–88%).

TABLE I. ALL Descriptive Factors (Using Original Nine Registries, 1973–1998)

	N
Age	
00–04	2290 (50%)
05–09	1148 (25%)
10–14	672 (15%)
15–19	509 (11%)
All ages	4619
Gender	
Male (%)	2635 (57%)
Female (%)	1984 (43%)
Ethnicity	
White	3820 (83%)
Black	339 (7%)
Other	436 (9%)

The percentages may not add to 100% due to rounding.

TABLE II. ALL Survival (Using Original Nine Registries, 1973–1998)

	N	1 year	5 year	Median
Age				
0–4 years	2290	94%	77%	> 10 years
5–9 years	1148	94%	74%	> 10 years
10–14 years	672	89%	59%	> 10 years
15–19 years	509	81%	42%	3.5 years
All Ages	4619	92%	70%	> 10 years
Gender				
Male	2635	92%	67%	> 10 years
Female	1984	92%	74%	> 10 years
Race				
White	3820	92%	71%	> 10 years
Black	339	90%	58%	> 10 years
Other	436	92%	71%	> 10 years

TABLE III. ALL Data for Children Under 5 Years of Age (Using Original Nine Registries, 1973–1998)

	Male			Female			
Age (years)	White	Black	Other	White	Black	Other	Total number
Descriptive data (no. of affected persons divided by age/gender/race)							
00	55	X	X	75	11	X	157
01	138	10	23	139	X	16	336
02	308	17	40	251	22	33	673
03	309	21	30	234	17	24	640
04	235	18	33	164	11	21	484
5-year survival (%)							
00	28	X	X	37	18	X	
01	76	60	90	73	X	79	
02	78	86	78	86	61	85	
03	82	50	84	88	88	87	
04	77	55	81	80	80	70	

X denotes those categories for which fewer than 11 cases were found.

Hispanics had the highest ALL incidence rate, $43/10^6$ vs. $28/10^6$ for non-Hispanics in 1992–98 (Tables III–V). While elevated, the relationship between incidence and age was similar for Hispanics as already described in the aforementioned races: 0–4 year olds $73/10^6$ person-years; 5–9 year olds $40/10^6$ person-years; 10–14 year olds $27/10^6$ person-years; 15–19 year olds $20/10^6$ person-years. The incidence rates differ significantly by sex (males $49/10^6$ vs. females $36/10^6$, $P < 0.0001$). The incidence of ALL in Hispanics over this short time period increased from $39/10^6$ (1993) to $49/10^6$ (1996), $P = 0.10$. There was no significant difference in 1-, 5-year-, or median survival between Hispanic and non-Hispanic children with ALL.

CONCLUSIONS

Childhood leukemia represents one of the success stories of modern pediatric oncology practice. Many articles have been written describing the treatment and specific molecular subgroupings that may aid in disease nosology [12–15]. Fewer articles have been written on the epidemiology of this disease in the US. Our review of children with ALL reported to a population-based registry does not suffer from ascertainment biases reflecting referral patterns to regional centers.

The data on Hispanic children in this study comes predominantly from Southern California. We do not have detailed information on specific country of origin for these children. It is known that Costa Rica has one of the highest incidence rates of childhood leukemia in the world [4], so it would be of interest to know how many of

TABLE IV. ALL in Hispanics (Using Eleven Registries, 1992–1998)

		Survival (%)		
	N	1 year	5 year	Median (yrs.)
Age				
00–04	395 (52%)	96	83	>7
05–09	178 (23%)	96	83	>7
10–14	108 (14%)	88	61	>7
15–19	79 (10%)	80	63	>7
All ages	760	93	78	>7
Gender				
Male (%)	445 (59%)	93	76	>7
Female (%)	315 (41%)	93	81	>7
Ethnicity				
White	749 (99%)			
Black	11 (1%)			

The percentages may not add to 100% due to rounding.

TABLE V. ALL Data for Hispanic Children Under 5 Years Old (Using Eleven Registries, 1992–98)

Age (years)	Male	Female	Total
Descriptive data (no. of affected persons divided by age/gender)			
00	20	12	32
01	42	29	71
02	58	49	107
03	63	50	113
04	42	30	72
5-year survival (%)			
00	50	+	59
01	76	95	84
02	73	81	76
03	93	98	95
04	86	83	85

+ designates a statistic, which could not be calculated.

the children in our study were of Costa Rican origin. The predominant countries of origin for Californian Hispanics differ from those of other areas, for example, New York City or Florida. It is unclear whether the finding of increased incidence among Hispanics would change if East Coast Hispanics were studied instead or in addition to West Coast Hispanics.

Many of our findings affirm previous reports of ALL, for example, the overall male predominance (1.3:1), young age at diagnosis (50% less than 5-year-old at diagnosis), worse survival for infants and teenagers [16–18]. Our detailed analysis of survival by age/sex/race reveals disparate survival times in Blacks, notably in Black children under 5 years old. Hispanic and White children have similar survival times. In particular, the survival times for black males are worse than those for any other group. The reason for this disparity is unclear. Considering that in the US, Hispanics and Blacks are socio-economically similar, we cannot explain the poorer survival for Blacks on the basis of such confounders as differing access to care or differing rates of early diagnosis. It is possible that the young black males have a different subtype of leukemia with a worse prognosis, and it has been suggested that individualization of treatment based on pharmacogenetic information may aid in reducing survival disparities [18].

Cancer registry data are limited to what is reported to registries, which in turn are based upon diagnoses rendered by multiple pathologists and hematopathogists with variable expertise and equipment.

Our data were collected during a time when the diagnostic features of ALL were being standardized and refined across the United States. While the basic diagnosis of ALL has not been altered, an increased knowledge of the importance of leukemic sub-classifications has been gained. The combination of cytogenetic analysis, molecular genotyping, and immunophenotyping of leukemic blasts provides important information related to prognosis and choice of therapeutic regimens.

We do not have information on subtypes of leukemia classifications. Genetic, environmental, and other pathogenic factors are beyond the data available to us, so we did not address them in this article. However, as molecular biologic techniques have improved, cancer registration practices have kept step. New cases registered using the ICD-O version 3 (begun January 1, 2001) include more information about subtypes of hematologic diseases. These data hold promise for future explorations of the relationship between ALL subtypes, race, and survival.

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